Group V: Claims 7-9, drawn to methods of detecting hypoxic cells by detecting protein;

Group VI: Claims 7 and 10, drawn to methods of detecting hypoxic cells by detecting mRNA;

Group VII: Claims 11-13, drawn to methods of detecting abnormal placental function in a mammal;

Group VIII: Claims 14 and 15, drawn to methods of screening by assaying cell invasiveness;

Group IX: Claims 14 and 16, drawn to methods of screening by assaying protein release;

Group X: Claims 19-20, drawn to methods of detecting proteins indicative of metastasis; and

Group XI: Claims 21-22, drawn to methods of identifying proteins indicative of an abnormal maternal placental interface.

In addition, the Examine alleged that the claims of Groups IV-VII are in an improper Markush format and required election of a particular species for examination. The Examiner further asserted that this is not an election of species (*see* Office Action, page 7, lines 2-3).

In response to this restriction requirement, Applicants provisionally elect Group V, claims 7-10, with traverse. With respect to Group V, Applicants provisionally elect species "C", protein C having a molecular weight of about 23 kDa and a pI of 7.5 with traverse.

A) The Examiner's restriction violated the guidelines of M.P.E.P. §803.02.

The Examiner's assertion that the Election of a particular protein comprising group V for examination is not an election of species is improper in light of M.P.E.P. §803.02. This section expressly states:

> This subsection deals with Markush-type generic claims which include a plurality of alternatively usable substances or members. In most cases, a recitation by enumeration is used because there is no appropriate or true generic language. A Markush-type claim can include independent and distinct inventions. This is true where two or more of the members are so unrelated and diverse that a prior art reference anticipating the claim with respect to one of the members would not render the claim obvious under 35 U.S.C. 103 with respect to the other member(s). **In applications containing claims of that nature, the examiner may require a provisional election of a single species prior to examination on the merits. The provisional election will be given effect in the event that the Markush-type claim should be found not allowable. Following election, the Markush-type claim will be examined fully with respect to the elected species and further to the extent necessary**

to determine patentability. If the Markush-type claim is not allowable over the prior art, examination will be limited to the Markush- type claim and claims to the elected species, with claims drawn to species patentably distinct from the elected species held withdrawn from further consideration.

The Examiner expressly alleged that "the different proteins and mRNAs are not obvious over one another, and a reference against any one of the recited molecules would not be a reference against any other of the recited molecules" (*see* Office Action, page 6, lines 19-22). **Under M.P.E.P. §802.03 this is precisely the situation in which may require a provisional election of species** (see emphasized text above).

The assertion by the Examiner that this is not an election of species runs contravenes the M.P.E.P. and thereby contravenes established P.T.O. practice and procedures. Accordingly the Examiner's assertion is improper and Applicants understand the restriction to be a restriction of species as provided in §803.02.

Accordingly, Applicants recognize that, per MPEP §809.02(c), to the extent all species fall within the limitations of a generic claim ultimately determined to be patentable, the non-elected species will no longer be deemed to be withdrawn and claims to the additional non-elected species will be considered by the Examiner.

B) The restriction between Groups V and VI is inappropriate.

The Examiner's allegation that the methods requiring detection of proteins (dependent claims 8 and 9) and nucleic acids (dependent claim 10) are improperly joined is simply incorrect. Independent claim 7 is directed to a method of detecting hypoxic cytotrophoblast cells or hypoxic chorionic villi by detecting a change in release of one or more enumerated proteins. Dependent claim 10 is directed to the same method in which the protein is assayed by assaying a nucleic acid encoding that protein. It is well known that nucleic acid levels (*e.g.* mRNA levels) are often a good surrogate for protein levels. Accordingly, claim 10 simply calls forth one of a number of possible methods of assaying release as provided in independent claim 7.

According to MPEP §803, the Examiner should examine all claims in an application, **even though they are directed to distinct inventions**, unless to do so would create a **serious burden**. In the instant case, a proper examination of claim 7 (included in both Group V and Group VI) requires the Examiner to consider that claim with respect to every possible method of assay release of the recited protein(s). Thus, a proper examination of the full scope of claim 7 implicitly involves an examination of

methods involving detection of nucleic acids. Examination of dependent claim 10 entails no greater burden than examination of independent claim 7. Accordingly the restriction between Groups V and VI is improper and should be withdrawn.

If the Examiner is proposing to examine claim 7 only with respect to methods of detecting proteins she is respectfully reminded that such an examination flatly contravenes accepted law. As stated by the CCPA:

> As a general proposition, an applicant has a right to have ***each claim*** examined on the merits.
>
> * * *
>
> **If, however, a single claim is required to be divided up and presented in several applications, that claim would never be considered on the merits. The totality of the resulting fragmentary claims would not necessarily be the equivalent of the original claim.** Further, since the subgenera would be defined by the examiner, rather than by the applicant, it is not inconceivable that a number of the fragments would not be described in the specification.
>
> * * *
>
> §121 provides the Commissioner with the authority to promulgate rules designed to *restrict* an *application* to one of several claimed inventions, ... It does not provide a basis under the authority of the Commissioner to *reject* a particular *claim* on that same basis.
>
> * * *
>
> We hold that a rejection under §121 violates the basic right of the applicant to claim his invention as he chooses. *In Re Weber, Soder and Boksay* 198 USPQ 328, 331-332 (CCPA 1978)

See also, *In Re Haas* 179 USPQ 623, 624, 625 (*In Re Haas I*) and *In Re Haas* 198 USPQ 334-337 (*In Re* Haas *II*).

The CCPA thus recognized that an Examiner **may not** reject a particular claim on the basis that it represents "independent and distinct" inventions. *See, In re Weber Soder and Boksay, supra.* Moreover, **the CCPA recognized that imposition of a restriction requirement on a single claim is just such an improper rejection.**

C) Restriction between Groups I through XI is improper.

As indicated above, according to MPEP §803, the Examiner should examine all claims in an application, **even though they are directed to distinct inventions**, unless to do so would create a **serious burden**.

In the instant case, claims 1-22 have already been searched and Examined (*see,* Office Action of January 11, 2000). If claims 1-22 have already been properly searched and examined, the present restriction is unnecessary as **there can be no serious burden where search and examination has already been performed**.

If the Examiner wishes to maintain the restriction between Groups I through XI, **Applicants would appreciate a written explanation as to why the previous search and Examination is to be ignored, and why the comments provided in the response filed on July 11, 2001 are not to be considered**.

Sequence Listing.

The Examiner indicated that the application is not in compliance with sequence rules, 37 C.F.R. §§ 1.821-1.825. In particular, the examiner noted that sequences falling within the definitions set forth by the rule are found at page 40. A disk containing the referenced sequence(s) in computer readable form, and a paper copy of the sequence information that has been printed from the floppy disk are provided herewith. The information contained in the computer readable disk was prepared through the use of the software program "PatentIn" and is identical to that of the paper copy.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 337-7871.

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Respectfully submitted,

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APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE IN 09/101,283 WITH ENTRY OF THIS AMENDMENT

In the specification:

In the claims:

8. A method of claim **[6]** 7, wherein the measurement is by direct determination of the protein.

9. A method of claim **[6]** 7, wherein the determination comprises the step of binding an antibody to the protein and determining the quantity of bound antibody present in a sample relative to the quantity of antibody bound to protein obtained from normoxic trophoblasts or normoxic chorionic villi.

10. A method of claim **[6]** 7, wherein the determination comprises detecting mRNA encoding any of the proteins and determining if the level of mRNA has changed relative to similarly treated normoxic cells.